Failure to Find P50 Suppression Deficits in Young First-Episode Patients With Schizophrenia and Clinically Unaffected Siblings

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Objective: To evaluate whether the P50 gating deficit is present in young first-episode patients with schizophrenia and their healthy young siblings. Methods: An auditory paired-click paradigm was used to assess P50 gating in 53 patients, 27 unaffected siblings, and 28 healthy controls. P50 parameters were compared between patients, sibs, and unrelated controls by a mixed-effects regression model. Results: P50 gating was not significantly impaired in patients with schizophrenia and healthy siblings as compared with controls. Conclusions: P50 gating was not found to be significantly impaired in young first-episode schizophrenia patients and in healthy young siblings. These results are in contrast with the existing literature. We suggest that P50 gating impairment may be developmentally or age dependent.

Key words: early psychosis/neurophysiology/relatives/endophenotype

Introduction

The P50 is an early positive component of the auditory averaged response, which is recorded at the vertex 50 ms after a click stimulus. When using a paired click paradigm with a 500-ms interval, a reduced P50 response after the second (test) stimulus compared with the P50 response after the first (conditioning) stimulus is expected. The P50 ratio is the amplitude of the P50 to the second stimulus divided by the amplitude of the P50 to the first stimulus. When subjects do not show a diminished response to the second stimulus, this suggests a failure of inhibitory mechanisms, also seen as a defect in sensory gating.1

Many studies have examined P50 ratio in patients with schizophrenia and a genetic linkage for the occurrence of this sensory gating defect to the α7-nicotinic receptor gene on chromosome 15q14 has been suggested.2 In 2004, a meta-analysis was published3 showing a P50 gating deficit in patients with schizophrenia across 21 studies. In this study, a high heterogeneity in effect size was found, but the authors could not detect the predictors of this heterogeneity.

The P50 event-related potential (ERP) has been viewed as a promising candidate endophenotype of schizophrenia. That is, a genetically influenced biobehavioral characteristic that will enhance the likelihood of identifying schizophrenia susceptibility.4 If the presence of such a characteristic would coincide with increased risk to develop schizophrenia, it should be present in excess of general population levels in the biological relatives of individuals with schizophrenia.4 Studies5–10 reporting on P50 ratios in relatives of patients with schizophrenia suggest P50 suppression to be an endophenotype for schizophrenia. To our knowledge, no P50 study in young first-episode patients with schizophrenia has been published. Considering the findings from previous studies3,5–10 and the possible effect of age on the presence of an endophenotype, we examined group differences between young, predominantly first-episode patients with schizophrenia and thoroughly screened young physically and mentally healthy siblings and controls.

Methods

Subjects

Subjects were 53 inpatients (mean age = 21.68, SD = 3.11, range = 17–29; 49 male, years of education = 11.83, SD = 2.1) of which 86.6% had a first episode of schizophrenia (7 patients had a second episode). A first episode of schizophrenia was defined as a period in which patients first met the criteria for schizophrenia and had not relapsed to a new psychotic episode. Patients’ reports on their symptoms were compared with the reports of their parents as described in patients’ case folders. The
diagnosis was determined by the Mini International Neuropsychiatric Interview Plus for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).11 This interview was also used to exclude affective disorders and substance abuse disorders and to determine the psychiatric history relevant to the inclusion criteria for both relatives and controls.

All patients were admitted to the Adolescent Clinic of the Academic Medical Centre (AMC) in Amsterdam. Two patients were medication naive, 45 were treated with atypical (5 patients where treated with clozapine), and 6 treated with typical antipsychotics (chlorpromazine [cpz] equivalent dose12,13 = 321.32 ± 243.30 mg). None of the patients reported to have used street drugs in the week before testing.

In addition, 27 unaffected siblings of the included patients (mean age = 22.7, SD = 3.98, range = 16–32; 11 male, years of education = 12.59, SD = 2.01) were recruited through written correspondence. Twenty-four families were represented by 1 sibling, 2 families by 2 siblings, and 1 family by 3 siblings. They were screened and considered psychiatrically healthy if they did not have a DSM-IV mood disorder, any psychotic symptom, or a substance abuse diagnosis and did not use cannabis. In addition, they were between the ages of 16 and 35 years; spoke Dutch fluently; and had no history of neurological disease nor a systemic disease known to involve central nervous system functioning, clinically significant head injury, or mental retardation. The healthy control group consisted of medically and psychiatrically healthy participants (n = 28, mean age = 21.86, SD = 2.95, range = 17–27; 22 males, years of education = 14.14, SD = 2.51) who were recruited from the community via advertisement posters. Inclusion criteria for controls were identical as for relatives, except that potential controls were excluded if they had a first-degree biological relative who had ever received psychiatric treatment. The control subjects received payment for their participation, whereas the other subjects did not. After complete description of the study to the participants, written informed consent was obtained.

The study protocol was reviewed by the Medical Ethics Committee of the AMC.

**P50 Procedure**

The electrophysiological examination was performed at the Department of Clinical Neurophysiology of the AMC. An initial series of continuing clicks was presented to determine the hearing threshold. Following the recommendation of Griffith et al.,14 the intensity was then set 50 dB above this threshold. The mean sound intensity was 75 dB and peak sound intensity was 85 dB. Clicks were produced with square pulses of 0.04-ms duration with an interval of 500 ms between conditioning and test stimulus. We used a computer program to elicit the auditory clicks. The program was set to present 72 click pairs with a random time interval of 8 or 9 seconds. In 3 cases, the program elicited more than 72 trials (73, 75, and 77). Subjects were comfortably laid down on a hospital bed in a sound- and light-attenuated room. They were instructed to relax, to keep their eyes open, and to listen to the clicks.

**Recording Method**

Electroencephalogram (EEG) was recorded with 21 surface Ag–AgCl disc electrodes applied with adhesive paste according to linked mastoids. P50 measurements were made from the vertex. Additionally, 4 electrodes were attached at the outer canthi of both eyes and above and below the left eye for the recording of eye movements. Electrode resistance was kept below 5 kΩ at all electrode sites. The EEG was recorded with a band-pass filter of 0.04–300 Hz, with a sampling rate of 1000 Hz.

Digitized data for each subject were stored in a database for subsequent off-line analysis using Brain Vision Analyzer (Brainproducts; http://www.brainproducts.com). The signals were digitally filtered with a low-pass filter of 50 Hz and a high-pass filter of 10 Hz (24 dB/oct) and were epoched at 50 ms prestimulus and 450 ms poststimulus. Conditioning trials with no discernable positive wave in the 100 ms poststimulus interval and trials with electrooculogram activity (eg, an eye blink), myogenic artefacts greater than 40 μV, or alpha wave activity during the recorded epoch were rejected.

An algorithm was used to identify and quantify the P50 component of the filtered mean EEG traces. The “conditioning” P50 wave was selected as the most positive peak between 40 and 80 ms after the first stimulus. The “test” P50 peak was then selected as the most positive wave in the latency range equal to the latency of the conditioning response plus or minus 10 ms. Amplitude was defined as the difference between the positive peak and the preceding negative peak through for both the conditioning and test P50 wave. The P50 ratio was calculated as the test P50 amplitude divided by the conditioning P50 amplitude times 100. This P50 ratio is thus a measure of the gating or inhibition of the P50 response, with lower values indicative of increased auditory sensory gating.

**Statistical Analysis**

P50 parameters were compared between patients, sibs, and unrelated controls by a mixed-effects regression model. We used this model to account for the family relationship between the patient and his/her siblings. In order to do this, we used family number as a random effect in the mixed-effects model. The fixed effect in the model was the group indicator (patient/sib/unrelated control). With this model, we estimated the average differences...
between the groups of patients, groups of sibs, and groups of unrelated controls but also the within- and between-family variances of the P50 parameters. The ratio of the between-family variance over the sum of the within- and between-family variances is called the intraclass correlation (ICC), which we used as a measure of similarity between the patients and their siblings. This might be viewed as due to the effect of shared environmental and genetic influences on the P50 parameters.

Cohen’s δ effect size was also reported. Correlation coefficients (Pearson’s r) were calculated between P50 ratio and age, years of education, gender, medication dosage (cpz equivalents), and sound intensity.

## Results

The mean of usable trials was 71.43 (patients: mean = 71.36, SD = 0.81, range = 69–75; siblings: mean = 71.22, SD = 0.58, range = 70–72; controls: mean = 71.75, SD = 1.18, range = 70–77). The mean number of lost trials was 1.32 for S1 and 1.48 for S2. The groups did not significantly differ on the number of lost trials (P = 1).

No statistically significant differences between the three groups were observed with respect to the latencies of the first response (F = 2.37; df = 2, 94.93; P = .1; ICC = 0.03) and second response (F = 2.04; df = 2, 63.25; P = .14; ICC = 0.11). The amplitudes of the first response (F = 0.11; df = 2; 58.65, P = .9; ICC = 0.56) and second response (F = 0.87; df = 2; 52.35; P = .43; ICC = 0.5) also did not differ between groups.

We did not find a significant difference between the groups on the absolute difference between S1 and S2 (F = 0.96; df = 2, 74.48; P = .39; ICC = 0.35). We did find a significant difference between the three groups on P50 ratio (F = 3.2; df = 2, 80.43; P < .05; ICC = 0.21) (Figure 1). However, post hoc t tests showed that patients performed worse than siblings as well as controls but did not reach significance (P > .1). P50 parameters for all groups are presented in Table 1.

P50 ratio was not significantly correlated with medication dosage (cpz equivalents) or with any other possible mediator such as age, gender, sound intensity, and educational level.

## Discussion

P50 gating was not found to be significantly impaired in young first-episode schizophrenia patients when compared with healthy controls. There was a trend for patients to perform worse; however, the difference with healthy controls was clearly smaller than in other P50 studies when compared with the mean meta-analytic effect size of δ = −1.56 found in the study of Bramon et al. Possible explanations may be the following: (1) the patients included were the youngest in literature, (2) 86.6% had a first episode of schizophrenia and a short duration of illness, and (3) most of our patients were on atypical neuroleptics that have been suggested to improve P50 performance in schizophrenia patients. Our control group was carefully matched on age and educational levels excluding these as possible confounders.

Second, in our study, siblings did not differ from controls on P50 ratio, and the intraclass correlation of 0.21 suggests that there is no evidence of shared environmental or genetic factors on P50 variation. This also is in contrast with the literature and might be explained by the young age of our sibling group in comparison to previously published studies which included parents or a mixed group of parents and siblings of older age. Another explanation might be that a cohort effect has occurred. The siblings who entered the study may represent a subpopulation of unaffected siblings and may be different from the siblings who where unwilling to take part in this study. We could not predict which sibling would be willing to take part in the study based on patient characteristics. We, however, did see a trend for Caucasian siblings to be more willing to take part in the study when compared with non-Caucasian siblings.

The finding that the P50 deficit is not present in young first-episode patients with schizophrenia, and in young siblings, suggests an effect of age on the P50 ERP. The P50 deficit may be the result of an ongoing neurodevelopmental-mental process independent of disease onset. Our findings are consistent with findings in the mismatch negativity (MMN) literature where first-episode patients also appear to have normal MMN’s in contrast to chronic patients with schizophrenia. In these studies, it

### Table 1. P50 Parameters for Patients (P), Healthy Siblings (S), and Healthy Controls (C)

<table>
<thead>
<tr>
<th></th>
<th>Patients' Mean (SD)</th>
<th>Siblings' Mean (SD)</th>
<th>Controls' Mean (SD)</th>
<th>Effect Size (δ) P – C</th>
<th>Effect Size (δ) S – C</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1 latency (ms)</td>
<td>55.6 (±7.97)</td>
<td>53.70 (±7.53)</td>
<td>57.9 (±5.97)</td>
<td>−0.31</td>
<td>−0.62</td>
</tr>
<tr>
<td>S1 amplitude (μV)</td>
<td>2.05 (±1.41)</td>
<td>2.18 (±1.44)</td>
<td>2.02 (±1.20)</td>
<td>0.03</td>
<td>0.12</td>
</tr>
<tr>
<td>S2 amplitude (μV)</td>
<td>1.11 (±1.05)</td>
<td>0.82 (±0.77)</td>
<td>0.93 (±1.01)</td>
<td>0.17</td>
<td>−0.12</td>
</tr>
<tr>
<td>Absolute difference</td>
<td>0.9 (±1.46)</td>
<td>1.36 (±1.33)</td>
<td>1.09 (±0.85)</td>
<td>−0.15</td>
<td>0.24</td>
</tr>
<tr>
<td>P50 ratio</td>
<td>65.02 (±55.82)</td>
<td>41.64 (±42.15)</td>
<td>43.13 (±38.22)</td>
<td>0.43</td>
<td>−0.04</td>
</tr>
<tr>
<td>Sample size (n)</td>
<td>53</td>
<td>27</td>
<td>28</td>
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has also been suggested that this may indicate ongoing neuropathological changes.

In our study, P50 does not meet the criteria for an endophenotype as the P50 deficit lacks in young patients and young siblings. The different studies reporting P50 deficits in older unaffected relatives, however, do suggest a change in older age related to vulnerability for schizophrenia and not just an age-related change. This might suggest that the P50 deficit is the result of an age-dependent genetic innovation. Longitudinal studies are necessary to test the hypothesis of an ongoing neurodevelopmental process as well as the hypothesis of an age-dependent genetic innovation.

Acknowledgments

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References


